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Annu Rev Entomol 1996;41:163-90

Ion channels as targets for insecticides.

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Ion channels are the primary target sites for several classes of natural and synthetic insecticidal compounds. The voltage-sensitive sodium channel is the major target site for DDT and pyrethroids, the veratrum alkaloids, and N-alkylamides. Recently, neurotoxic proteins from arthropod venoms, some of which specifically attack insect sodium channels, have been engineered into baculoviruses to act as biopesticides. The synthetic pyrazolines also primarily affect the sodium channel, although some members of this group target neuronal calcium channels as well. The ryanoids have also found use as insecticides, and these materials induce muscle contracture by irreversible activation of the calcium-release channel of the sarcoplasmic reticulum. The arylheterocycles (e.g. endosulfan and fipronil) are potent convulsants and insecticides that block the GABA-gated chloride channel. In contrast, the avermectins activate both ligand- and voltage-gated chloride channels, which leads to paralysis. At field-use rates, a neurotoxic effect of the ecdysteroid agonist RH-5849 is observed that involves blockage of both muscle and neuronal potassium channels. The future use of ion channels as targets for chemical and genetically engineered insecticides is also discussed.

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Eur J Drug Metab Pharmacokinet 1997 Jul-Sep;22(3):211-6

Skin distribution of fipronil by microautoradiography following topical administration to the beagle dog.

Cochet P, Birckel P, Bromet-Petit M, Bromet N, Weil A

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To investigate the localisation of fipronil in dog skin, [14C]-fipronil was topically applied to a male beagle dog (spot-on administration) at the therapeutic dose of 10 mg/kg. By means of autohistoradiography, the radioactivity was precisely detected in the skin and appendages at various intervals after application. Radioactivity was predominantly observed within the stratum corneum, the viable epidermis, and in the pilo-sebaceous units (mainly in the sebaceous glands and epithelial layers). [14C]-fipronil was significantly detected in these structures up to 56 days post-treatment, in the application zone (neck) but also in the lumbar zone, thus indicating the mechanical displacement of fipronil. No radioactivity was detected in either the dermal or the hypodermal layers, confirming the low percutaneous passage of fipronil.

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Chem Res Toxicol 1998 Dec;11(12):1529-35

Mechanisms for selective toxicity of fipronil insecticide and its sulfone metabolite and desulfinyl photoproduct.

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Fipronil, an N-phenylpyrazole with a trifluoromethylsulfinyl substituent, initiated the second generation of insecticides acting at the gamma-aminobutyric acid (GABA) receptor to block the chloride channel. The first generation includes the polychlorocycloalkanes alpha-endosulfan and lindane. In this study, we examine the mechanisms for selective toxicity of the sulfoxide fipronil and its sulfone metabolite and desulfinyl photoproduct relative to their target site interactions in vitro and ex vivo and the importance in fipronil action of biooxidation to the sulfone. Differences in GABA receptor sensitivity, assayed by displacement of 4'-ethynyl-4-n-[2, 3-3H2]propylbicycloorthobenzoate ([3H]EBOB) from the noncompetitive blocker site, appear to be a major factor in fipronil being much more toxic to the insects (housefly and fruit fly) than to the vertebrates (humans, dogs, mice, chickens, quail, and salmon) examined; in insects, the IC50s range from 3 to 12 nM for fipronil and its sulfone and desulfinyl derivatives, while in vertebrates, the IC50 average values are 1103, 175, and 129 nM for fipronil, fipronil sulfone, and desulfinyl fipronil, respectively. The insect relative to the vertebrate specificity decreases in the following order: fipronil > lindane > desulfinyl fipronil > fipronil sulfone > alpha-endosulfan. Ex vivo inhibition of [3H]EBOB binding in mouse brain is similar for fipronil and its sulfone and desulfinyl derivatives at the LD50 dose, but surprisingly, at higher doses fipronil can be lethal without detectably blocking the [3H]EBOB site. The P450 inhibitor piperonyl butoxide, acting in houseflies, increases the metabolic stability and effectiveness of fipronil and the sulfone but not those of the desulfinyl compound, and in mice it completely blocks the sulfoxide to sulfone conversion without altering the poisoning. Thus, the selective toxicity of fipronil and fipronil-derived residues is due in part to the higher potency of the parent compound at the insect versus the mammalian GABA receptor but is also dependent on the relative rates of conversion to the more persistent and less selective sulfone metabolite and desulfinyl photoproduct.

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